REMARKS

1. ***Substitute Specification***

As requested by the Examiner, applicants submit herewith a substitute specification, including the description and an amended set of claims. This amendment follows the revised format announced in the Pre-OG notice of January 31, 2003, with the changes from the previous version being indicated by strikethrough and underlining.

The application as originally filed included pages 1-31 of the specification, page 32 with a legend to the drawing figures, and sheets identified as "Amended Sheet" for pages 17 and 18 and 27-31. The "Amended Sheets" represented Article 34 amendments that were made during International Preliminary Examination of the PCT application from which this national phase application derives. The substitute specification that is submitted herewith incorporates the "Amended Sheets" into the specification, and also incorporates the amendments made in the Preliminary Amendment submitted at the time of filing. Since these are all previous amendments, they are not highlighted in the substitute specification. Amendments have been made to the claims in response to the points made by the Examiner in the Official Action, and these new amendments are indicated by strikethrough and underlining.

2. ***The invention as claimed***

The subject matter of the invention as claimed in claim 1 or claim 2 is a transfection composition characterized in that it consists essentially of:

1. **the chemical substance to transfect** into eukaryotic cells (nucleic acids, proteins, peptides or other chemical substances), and

2. **a transfecting peptide** consisting of:

    i) an NLS sequence (from the adenovirus fiber or the SV40 VP3 protein) linked to,

    ii) a hydrophobic sequence from the adenovirus fiber corresponding to X_1-F(D/N)PVYPY-X_2, said peptide comprising or being associated to,

iii) a sequence of basic amino acids or a cationic polymeric sequence or a polyalcohol.

The invention describes the transfecting peptides **AKRARLSTSFNPVYPYEDES-K_{10}** and **AKRARLSTSFNPVYPYEDES-K_{20}** corresponding to positions 3 to 22 of the adenovirus type 3 (Ad3) fiber amino acid sequence (figure 7 of the present Application) linked to a polylysine sequence, wherein the NLS (underlined) and the hydrophobic (in bold) sequences correspond respectively to positions 3 to 7 and 8 to 22.

It clearly emerges from the invention, and especially from the comparative data presented in Table II page 19, that the combination of the above features i), ii) and iii) of the transfecting peptide is necessary and sufficient to confer a peptide the ability to transfect nucleic acids (plasmid DNA encoding the luciferase gene for instance) into eukaryotic cells; this means that when a composition containing the above defined peptide and the plasmid DNA only is contacted with eukaryotic cells, the plasmid DNA is internalized into the cytoplasm of the cells and is released in the nucleus where, in the above example, the lucifcrase gene is transcribed.

3. ***Analysis of the prior art citations***

- Signas et al., J. Virol., 1985, 53, 672-678 (D1)
  D1 discloses the complete nucleotide and amino acid sequences of the adenovirus type 3 fiber gene (figure 2 of D1), which confirms the structure of the fiber protein established for other adenovirus serotypes.

- Kajon et al., Virolo, 996, 215, 190-196 (D2)
  D2 discloses the complete nucleotide and amino acid sequences of an adenovirus type 7 human isolate fiber gene and its comparison with that of other adenovirus serotypes (figure 4 of D2).

- PCT Application WO 97/18317 (ll3)
  D3 discloses transfection compositions consisting essentially of:

1. **the chemical substance to transfect** into eukaryotic cells (nucleic acids, proteins, peptides or other chemical substances), and

2. **an adenoviral protein complex** for transfecting nucleic acids, proteins, peptides or other chemical substances into eukaryotic cells called also **dodecahedron**, which consists of **12 pentons** (fiber and penton base) or **12 penton bases.**

The PCT Application WO 97/18317 shows that the dodecahedron structures with or without the adenovirus fiber represent new vectors for gene therapy (page 2, lines 7 to 31) since they are internalized efficiently into the cytoplasm of eukaryotic cells and localize at the cytoplasmic surface of the nuclear membrane (example 2, figures 8, 9 and 10).

In some preferred embodiment, the chemical substance is bound to the protein complex via a bi-functional peptide (bi-functional peptide ligand) wherein:

- the N-terminal part of the bi-functional peptide consists of the N-terminal amino acid sequence from the adenovirus fiber which corresponds to the zone of attachment to the adenoviral protein complex (page 4, lines 17-1.9) that allows binding of the N-terminal part of the bi-functional peptide to the protein complex, and

- the C-terminal part of the bi-functional peptide consists of a polylysine or a polyarginine sequence (page 4, lines 15 to 36) which allows binding to the DNA via a temporary bond such as a ionic bond which can be destroyed and thus allows the passage of the DNA into the nucleus where gene expression takes place (page 3, line 66 to page 4, line 2).

More precisely, example 3 page 14 lines 11 to 14 discloses a transfection composition consisting of:

1. the plasmid DNA to transfect (pGL3) chemical substance to transfect into eukaryotic cells (nucleic acids, proteins, peptides or other chemical substances),

2. adenovirus serotype 3 dodecahedrons, with or without fiber (page 14, line 10), and

3. bi-functional peptide(s) (SEQ ID NO : 5 to 9, page 13, lines 37 to 67 and page 14, line 11-12) consisting of the amino-acid sequence corresponding to positions 3 to 22 (**AKRARLSTSFNPVYPYEDES**) or 11 to 22 **(SFNPVYPYEDES)** of the adenovirus fiber, linked to a polylysine (K_{20}) or a partial or complete core protein sequence.

Example 4 and figure 12 (A and B) show that the bi-functional peptide acts as a bi-functional lipgand which attaches to the dodecahedron and to the plasmid and modifies the DNA whose structure becomes compact.

Figure 11 shows that the transfection compositions containing DNA bound to dodecahedrons via a bi-functional peptide are as active as adenovirus for transfecting DNA into eukaryotic cells.

4. Irrelevance of D1, D2 and D3 as regards novelty and obviousness of the transfecting peptide according to the present invention

Novelty

Dl and D2

Signas et al. and Kajon et al. which do not disclose any transfection composition containing a transfecting peptide derived from the adenovirus fiber are not pertinent as regards novelty of the present invention.

D3

The transfection composition disclosed in the PCT Application WO 97/18317 wherein the transfecting agent consists of an adenovirus protein complex formed by 12 pentons or 12 pentons bases (dodecahedrons) is different from the transfection composition according to the invention, wherein the transfecting agent is a peptide derived from the adenovirus fiber.

Thus the transfection composition as claimed in claims 1-3 and 5-10 is novel in view of the prior art cited.

Obviousness

The transfecting peptide according to the present invention is not obvious in view of the prior art cited since nothing in these documents suggest that **the peptide AKRARLSTSFNPVYPYEDES-K_{20} alone, is able to be internalized into the cytoplasm of eukaryotic cells and thus represents a transfecting peptide which can be used as a vector for gene therapy:**

- D1 and D2 which disclose adenovirus fiber sequences are totally silent as regards eukaryotic cells transfection.

- D3 indicates that:

  1) adenovirus dodecahedrons are essential for internalization of a chemical substance into eukaryotic cells, and

  2) the N-terminal sequence of the adenovirus fiber containing amino acids 11 to 22 acts which is able to bind to the dodecahedrons can be used in combination with a polylysine sequence (K_{20}) to immobilize DNA onto the adenoviral dodecahedron vector.

4. Unity of invention

Claim 4 has been withdrawn from consideration by the Examiner as being drawn to a nonelected invention. Applicants have retained claim 4 in the application and request the Examiner to reconsider and withdraw the election requirement if an allowable generic claim is found.

Moreover, Applicants request the Examiner to reconsider and withdraw the election requirement. From the foregoing discussion of the prior art, it clearly emerges that the transfection composition as claimed in claim 1 or claim 2 shares a significant structural element (transfecting peptide derived from the adenovirus fiber) which is distinct (novel and not obvious) from the prior art (adenoviral dodecahedron transfecting protein complex disclosed in the PCT Application WO 97/18317). Therefore the claimed alternative meets the requirement of Unity of invention (Rule 13.2 PCT), according to Section (1) (i) (B) and (ii) of Annex B of the Administrative instructions under the PCT. Consequently, the subject matter of claims 1 and 2 form a single general inventive concept (Rule 13.1 PCT). Since the Examiner's decision, although final, is based on incorrect grounds, we ask the Examiner to reconsider his position as regards Unity of Invention.

5. Conclusions

Rejection of claims 1-3, 5-6, 9, 10 under 35 U.S.C. § 102(b) (Pages 3-4 of the Office Action)

In view of the foregoing discussion and the claim amendments, it is clear that claims 1-3, 5-6, 9, 10 are novel in view of the prior art cited and thus satisfy 35 U.S.C. 102 (b).

Rejection of claims 1-3 and 5-10 under 35 U.S.C. § 112 second paragraph (Pages 4-6 of the Office Action)

These objections no longer apply to the new claims in which all the vague and indefinite expression have been either amended or deleted.

Formal notification of the allowability of all claims as now present is solicited.

Respectfully Submitted,

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CLT01/4577878v2